COMMUNICATIONS

PATHOLOGY OF TRABECULAR NERVES IN OPEN-ANGLE GLAUCOMA*†

BY

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ADVANCED degenerative nerve fibre pathology is found all through the trabeculae of both eyes of a patient with well-documented open-angle glaucoma. These findings substantiate the nerve fibre changes described in both eyes of another case of open-angle glaucoma (Wolter, 1959a).

Innervation of the normal trabecula by delicate branching nerve fibres ending with free terminals without special end-formations has been demonstrated by conventional histological techniques (Vrabec, 1954; Holland, von Sallmann, and Collins, 1956; Kurus, 1958; Wolter, 1959b) as well as by electron microscopy (Feeney, 1961). The role of these trabecular nerves within the functions of the outflow apparatus is not yet known.

Definite pathology of the trabecular nerves has been observed in both eyes of one case of well-documented unoperated open-angle glaucoma (Wolter, 1959). As long as not even the normal functions of the trabecular nerves are known it is premature to discuss the significance of their pathology. However, the accumulation of such findings is essential for progress in understanding glaucoma.

Case Report

A 60-year-old male Negro was first seen on February 6, 1959, at Wayne County General Hospital with carcinoma of the ascending colon with metastases.

Examination.—His first eye examination on February 18, 1959, showed the visual acuity to be 20/30 in the right eye, and 20/100 in the left, with correction. Increased bilateral intra-ocular pressure (30.8 mm. Hg (Schiötz) with 5.5 and 10 g. weights) was observed at this time. Deep cupping of the optic discs—more advanced in the left than in the right—was observed with the ophthalmoscope. Treatment with pilocarpine eye drops and eserine ointment successfully brought the intra-ocular pressure down to normal. Gonioscopy on April 24, 1959, revealed open angles with visible scleral spurs in both eyes. On April 27 the visual fields on the right side were found to be normal while an

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extensive upper field defect on the left side was compatible with advanced glaucoma. A water-drinking test (1,000 ml. water at 9.55 a.m.) done on April 27 supported the diagnosis of bilateral open-angle glaucoma:

Time (min.)	Pressure (mm. Hg)	
	Right	Left
0	27.2	24.4
15	31.6	29.0
30	31.6	31.6
45	27.2	29.0
60	27.2	29.0
120	27.2	27.2

The patient was seen at regular intervals and his pressure was known to be controlled until June, 1959. A 9-month interval without examination or treatment elapsed before the patient came back on May 25, 1960, when the central vision was 20/80 in each eye. The intra-ocular pressure was 42 mm. Hg (Schiötz) in each eye. Gonioscopy showed the angle in both eyes still to be open. The visual field examination revealed loss of the whole periphery in both eyes with only small islands of central vision remaining. Treatment with pilocarpine and eserine was resumed, but was no longer sufficient to bring the pressure to normal. Diamox was added. No surgery was considered because of the patient's progressive metastatic carcinoma. He was seen for the last time before his death on November 23, 1960, when his vision was 20/80 in the right eye and 20/200 in the left, and the pressure was 22.5 mm. Hg (Schiötz).

Result.—The patient died of metastatic carcinoma on January 2, 1961.

Both eyes were injected with ammonium bromide formalin (Cajal solution) 5 hours after death and obtained for pathological study.

Method of Horizontal Examination.—Both eyes were cut in half horizontally. One half of each eye was imbedded in paraffin, cut, and stained with haematoxylin and eosin. Of the other halves tangential sections (Flocks, 1956) of the areas of the anterior chamber angles were cut on the freezing microtome. These sections were stained for nerves with the double-impregnation technique and the three-fold method of del Rio Hortega (Scharenberg and Zeman, 1952).

Pathological Description.—Both eyes are normal in size and shape. Glaucomatous excavation of the disc is seen in both eyes after they are cut open.

The microscopic examination of the paraffin sections reveals virtually the same pathological changes in both eyes, and the findings in both eyes are discussed simultaneously in the following. The corneal epithelium is continuous in both eyes and of normal thickness. However, there are a few areas of bullous epithelial change. Bowman's membrane is normal and continuous. The corneal stroma shows no pathology. Descemet's membrane is normal and exhibits some peripheral Hassall-Henle bodies. The corneal endothelium shows some atrophy in both eyes. The anterior chamber appears to be of about normal depth in both eyes. The filtration angle is open. In the routine sections the trabecula appears somewhat cellular and of dense structure in both eyes (Fig. 1, opposite).

FIG. 1.—Area of filtration angle of left eye. Haematoxylin and eosin. $\times 150$.

There also is extensive pigment all through the trabecula. Schlemm's canal is open. The iris shows heavy pigmentation and is normal. No lens pathology is seen in either eye. The ciliary processes exhibit some early fibrosis, but no pathology is found in the ciliary body area. Both eyes show some peripheral cystic degeneration of the retina. All through the retina of both eyes the nerve fibre layer is decreased in thickness and only a few ganglion cells are left in the ganglion cell layer. All other layers of the retina appear normal. Both optic discs are excavated and show atrophy of the nerve fibre layer at its margin as well as atrophy of the nerve fibre bundles in the optic nervehead and in the optic nerve itself. The central retinal vessels are fibrotic and small, but open in both eyes. The pigment epithelium of both eyes shows some drusen of the senile type, but is otherwise normal. The choroid is thin and atrophic and shows no pathology. The sclera is normal.

Extensive pigment deposition throughout the trabecula can be verified by light silver stain (Fig. 2, overleaf).

With the three-fold silver technique, a good demonstration of the trabecular sheets is obtained (Fig. 3, overleaf).

No granularity of the trabecular collagen is found in either eye (cf. Teng, Paton, and Katzin, 1955). The trabecular endothelium contains pigment granules in many areas, but is devoid of vacuolization (so called "foamy" degeneration).

A multitude of terminal nerve fibres can be observed in the trabecula of each eye. At first one gains the impression that the trabecula of this case contains more nerve fibres than normal. Careful study, however, shows that very irregular coarse and bizarre swellings of most nerve fibres convey a false impression. Their number is not actually increased.

FIG. 2.—Area of filtration angle of left eye after very light silver impregnation. Extensive pigment deposition is seen in the trabecular network (arrow). The scleral spur (S) can be recognized. Hortega stain. $\times 150$.

FIG. 3.—Trabecular sheets as seen in a tangential section of the left eye. The trabecular collagen appears normal. Pigment is seen to be deposited in the spaces. Hortega stain. $\times 500$.

Fig. 4 shows abnormal nerve fibres in the trabecula of the right eye.

FIG. 4.—Many abnormal nerve fibres of abnormal course and calibre at base of trabecula of right eye (arrows). Tangential section, Hortege stain. $\times 1000$.

Fig. 5 and Fig. 6 (overleaf) show the small terminal swellings of interrupted nerve branches and nerves taking devious courses.

FIG. 5.—Nerve fibres in trabecula of right eye distorted into a bizarre kinked pattern and bifurcating like the branches of an oak tree (arrows). Tangential section, Hortege stain. $\times 1000$.

FIG. 6.—Generalized thickening and irregular course of nerve fibres (arrows) in trabecula of right eye. Tangential section, Hortega stain. $\times 1,000$.

A large terminal nerve swelling of bizarre shape is seen in Fig. 7.

FIG. 7.—(a) Very large terminal swelling of bizarre shape (T) of a thickened nerve fibre (N) in the trabecula of the right eye. Groups of normal appearing trabecular nerves also appear in the picture (arrow). Tangential section, Hortega stain. $\times 650$. (b) Diagrammatic reconstruction to explain photomicrograph in Fig. 7a.

A medium-sized terminal nerve swelling of simple globular shape at the base of the trabecula is seen in Fig. 8.

FIG. 8.—Degenerative end-bulb of round shape of an interrupted nerve fibre (arrow) in trabecula of right eye. Tangential section, Hortege stain. $\times 1,000$.

Nerve fibres entering the trabecula from the side of the scleral spur are seen in Fig. 9. One of these appears abnormally thickened, and those next to it are normal.

FIG. 9.—Nerve fibres entering trabecula from side of scleral spur. One appears abnormally thickened (arrow). Tangential section, Hortege stain. $\times 1,000$.

Occasionally degeneration of single nerves with development of local globular thickening is found in the ciliary plexus (Fig. 10).

FIG. 10.—Nerve bundle in ciliary plexus of left eye. One nerve shows globular degeneration (arrow). Hortega stain. $\times 1,000$.

In most instances, however, the elements of the ciliary plexus of both eyes appear to be normal (Fig. 11).

FIG. 11.—Normal appearing nerve fibres from ciliary plexus of right eye. Melanocytes are seen to surround the nerve fibre bundles. Hortega stain. $\times 1,000$.

Comment

Distinct nerve fibre pathology has now been demonstrated by us all through the trabeculae of four eyes of two patients with well-documented unoperated open-angle glaucoma. The total picture of the nerve fibre changes observed in these eyes impresses us as quite characteristic and we have not seen anything like it in the trabecula in other types of glaucoma (Wolter, 1960). Four pathological details comprise the nerve changes seen in the trabeculae of these four eyes with open-angle glaucoma:

(1) The normal regular course of the trabecular nerves is distorted into a bizarre kinked pattern. The normally acute angle at which trabecular nerves bifurcate becomes more obtuse like the branching of an oak tree.

(2) Most nerve fibres show some degree of generalized thickening. There also are local spindle-shaped as well as globular enlargements in the course of some nerves.

(3) Degenerative end-bulbs of round shape and of a size commonly seen as a result of nerve fibre interruption all through the peripheral nervous system are common in the trabeculae of these eyes.

(4) All cases show peculiar very large terminal swellings of very irregular shape at the end of interrupted trabecular nerves. Degenerative formations of this type are very unusual.

It is our impression that the nerve fibre changes described above are a true part of the pathology of the trabeculum in these cases of open-angle glaucoma. However, further conclusions as to the significance of this trabecular nerve pathology at this time are unwarranted.

A bizarre trabecular nerve formation much like those found by us in open-angle glaucoma (*cf.* Wolter 1960, Fig. 29) has been photographed by Kurus (1958, Fig. 6); see also Duke-Elder and Wybar (1961, Fig. 250). Kurus called this a sensory nerve ending, but offered no clinical or pathological data concerning this eye. Thus, it seems possible that the eye with this formation may have had unrecognized glaucoma. This possibility is supported by the fact that a large terminal swelling of an interrupted trabecular nerve is seen next to the bizarre nerve formation in Kurus's beautiful microphotograph.

It is of great interest for the present study that Bárány (1962) has recently shown that in rabbits adrenolytic substances abolish the transient increase of the outflow facility produced by cervical gangliotomy. Bárány concludes from this that α -adrenergic substances released from ciliary body or iris produce this effect on a non-vascularized structure, presumably the trabecular meshwork. It seems possible to us that the trabecular nerves—the function of which is still totally unknown—may play an active part in this process.

Ashton (1960) accepts the presence of nerve endings in the normal human trabecula with the possible function of baroreceptors or regulators of outflow as postulated by Carpenter (1957). Denervation experiments on rabbits by

Holland, von Sallmann, and Collins (1957) indicate that the nerves of the trabecular meshwork originate from at least three sources: the sympathetic (*via* the superior cervical ganglion), the parasympathetic (*via* the ciliary ganglion), and the fifth cranial nerve. The discovery by Armaly that stimulation of the ciliary ganglion causes increased outflow facility (Armaly and Burian, 1957; Armaly, 1959) is of particular significance in that we know the ciliary ganglion contributes predominantly parasympathetic nerve fibres to the trabecula. Whether these parasympathetic nerves are efferent or afferent or both is an unsolved problem. All these facts indicate that pathology of the nerves supplying the trabecula in open-angle glaucoma is of great interest—even if it should turn out to be secondary to an unknown primary glaucomatous process.

Summary

Advanced nerve fibre pathology is shown all through the trabeculae of both eyes of a patient with unoperated open-angle glaucoma. These nerve changes are very similar to those observed in both eyes of an earlier case.

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